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ACUTE ALBUMIN-INDUCED PLASMA VOLUME EXPANSION AND HEAT EXPOSURE--ETC(U)  
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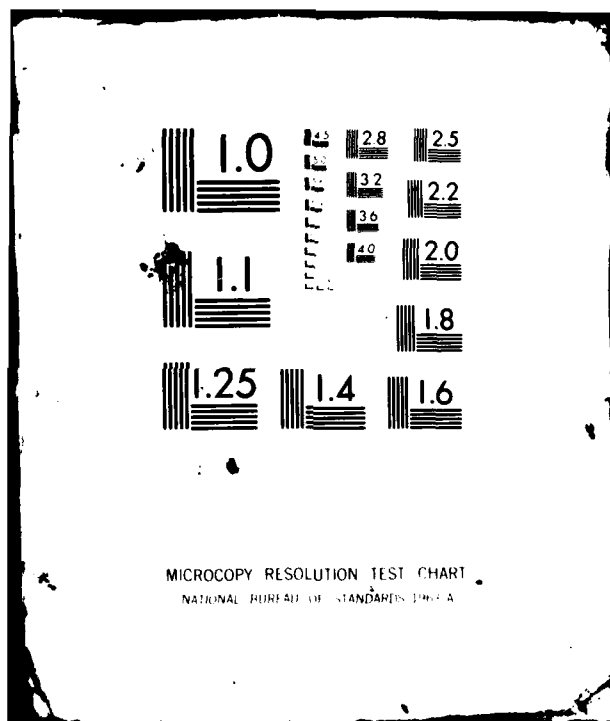
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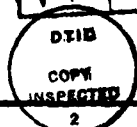
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Even the finely controlled diurnal/nocturnal periodicity of cortisol and aldosterone secretion were unaffected by heat stress or volume expansion, but there did occur a significant reduction in plasma levels of aldosterone as a result of albumin-induced plasma volume expansion. No changes were observed in circulating angiotensin I (plasma renin activity) or arginine-vasopressin (antidiuretic hormone). We concluded that the duration and intensity of heat stress used in these studies had no effects on plasma hormonal levels and periodicities, but plasma volume expansion elicited a significant decrement in aldosterone concentrations.

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**Acute Albumin-Induced Plasma Volume  
Expansion and Heat Exposure: Hormonal Responses in Men**

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### Abstract

To determine the effects of acute plasma volume expansion and heat exposure on hormonal responses in men, two doses of albumin were administered intravenously followed by exposure to heat stress (37°C, 30-35% RH). Plasma volume was previously established by a dye dilution technique using indocyanine green. During heat exposure blood samples were taken from antecubital catheters at 1,3,6,9,12 and 24 hours following completion of albumin or saline (control) infusion, and the plasma analyzed for several hormones. No significant effects of heat stress or albumin administration were noted on circulating cortisol concentrations. Even the finely controlled diurnal/nocturnal periodicity of cortisol and aldosterone secretion were unaffected by heat stress or volume expansion, but there did occur a significant reduction in plasma levels of aldosterone as a result of albumin-induced plasma volume expansion. No changes were observed in circulating angiotensin I (plasma renin activity) or arginine-vasopressin (antidiuretic hormone). We concluded that the duration and intensity of heat stress used in these studies had no effects on plasma hormonal levels and periodicities, but plasma volume expansion elicited a significant decrement in aldosterone concentrations.

**Key Words:** heat stress, albumin-induced volume expansion, cortisol, aldosterone, angiotensin I, vasopressin

### Introduction

Heat acclimatization in humans is accompanied by a reduced heart rate and rectal temperature as well as the secretion of a more dilute sweat during rest and exercise in the heat (2,3). Generally, this reduced physiological cost of exposure to heat stress has been attributed to increased cardiovascular efficiency and plasma volume expansion (3,22,26) preceding subsequent thermoregulatory benefits (2). Senay (23, 24) later attributed these responses to an influx of interstitial protein and water into the circulatory system, pursuant to increased capillary permeability and protein availability. Thus, the increased cardiovascular and thermoregulatory benefits of heat acclimatization can be partially attributed to the increased plasma volume.

Since albumin is the chief proteinaceous constituent of plasma and hence plays the major role in maintaining fluid volume in the circulatory system, we hypothesized that intravenous administration of large albumin doses would be accompanied by an increase in plasma oncotic pressure which, in turn, would act to draw interstitial fluid into the circulatory system. Thus, in hours we could simulate the plasma volume expansion of heat acclimatization ordinarily occurring over several days. Such an experimental tool would not only permit us to study the role of increased plasma volume in reducing the stress induced by heat exposure, but also provide us with a model to investigate the hormonal and other responses critically important to the acclimatization process.

The fluid regulatory hormones, aldosterone, antidiuretic hormone (vasopressin) and renin-angiotensin, as well as cortisol, have all been reported to be affected during acute and chronic exposure to environmental heat stress (1,11,19). Increments in the circulating levels of any of these hormones could be related to an adaptational response designed to maintain or increase body fluid levels. While Finberg et al. (9,10) have reported that heat acclimatization

attenuated the normal heat-induced elevation in plasma renin activity, Davies et al. (8) found no effects of acclimatization on the increments of either plasma renin activity or aldosterone, but these responses were reduced by ingestion of dilute saline solution. Earlier, Braun et al. (4) had demonstrated that exogenous aldosterone administration to human test subjects had beneficial effects on several indices of heat acclimatization, including heart rate and rectal temperature, during exercise in the heat. Thus, the expansion of fluid volume during heat acclimatization may be dependent upon adequate adaptational responses of the fluid regulatory hormones.

We were thus interested in whether the degree and persistence of plasma volume expansion elicited by acute heat exposure and albumin administration were closely related to adaptational hormonal responses. Further, our experimental protocol permitted comparison between two levels of plasma volume expansion as well as a hot and a moderate environmental temperature. Finally, serial blood sampling over a 24 hour period allowed an evaluation of the more subtle effects on diurnal/nocturnal periodic oscillations of plasma constituents (20,25), especially the adrenocortical hormones.

#### Materials and Methods

Twenty-seven healthy male volunteers participated in these studies after giving their free and informed voluntary consent to all of the test procedures. Their mean age was  $25 \pm 5$  ( $\bar{X} \pm SD$ ) years; their mean weight and height were  $74.6 \pm 10.8$  kg and  $177 \pm 7$  cm, respectively. Test subjects (Ss) retained the right to withdraw from the study for any reason at any time, but none exercised this option.

Test volunteers reported to the laboratory on the day prior to an experimental test for physical examinations, medical histories, and



determination of plasma volumes. Plasma volumes were quantitated by a dye dilution technique using indocyanine green. Following these preliminary procedures Ss were allowed to leave the laboratory for the evening meal, and later returned to spend the night in a chamber maintained at 25°C, 40% RH. They were awakened at 0600 the following morning and were either removed to a second environmental chamber maintained at 37°C, 30%RH or allowed to remain for the next 26 hours under the moderate environmental conditions of the previous night.

At approximately 0800h each test subject was fitted with a small catheter in an antecubital vein for administration of 25 g (100 ml) or 50 g (200 ml) of sterile albumin (Alb) solution. The albumin was prepared and supplied by the American Red Cross. Before administration a blood sample (10 ml) was taken to establish control (time 0) levels of the hormones under investigation. Albumin was administered at a rate of 2-3ml/minute; thus, infusion required up to 1.5 h in the case of the high dosage. Under either environmental condition (i.e. 25°C or 37°C) each test subject received either the high or low dosage of albumin and sterile, non-pyrogenic saline (Sal) equivolumetrically. Thus, 4 groups of test subjects were used: group 1, 25°C - 100 ml; group 2, 25°C - 200 ml; group 3, 37°C - 100 ml; group 4, 37°C - 200 ml. The saline and albumin doses were separated by at least a two-week interval.

One hour following completion of the infusion procedure a second blood sample (10 ml) was removed, and the process repeated at 3,6,9,12, and 24 h post-infusion. The blood was quickly processed and deep-frozen (-30°C) for subsequent analysis. Test subjects were confined to either test chamber for this 24 h interval; sedentary activities were permitted. All food, recreational and sanitational facilities were provided within the chamber. Volunteers were encouraged to drink 500 ml of citrus-flavored, non-carbonated beverages during

the waking hours; they slept from 2300-0630 h. Experiments were conducted between February and April to minimize any natural seasonal acclimatization.

Aliquots of the frozen plasma were assayed by radioimmunoassay procedures for cortisol, aldosterone, renin activity (angiotensin I), and arginine-vasopressin. Cortisol was measured with radioimmunoassay test kits purchased from Damon Diagnostics, Needham, MA; aldosterone radioimmunoassay test kits were likewise obtained from Damon, but were manufactured by International CIS, Sorin-Biomedica, Saluggia, Italy. Angiotensin I (plasma renin activity) was analyzed using radioimmunoassay test kits produced by New England Nuclear Corp., No. Billerica, MA. All of these assays were performed in accordance with procedures outlined in the respective technical bulletins; a maximum of 100  $\mu$ l plasma was utilized. Arginine-vasopressin was assayed essentially by the methods of Hammer (16);  $^{125}$ I arginine-vasopressin was purchased from New England Nuclear, and vasopressin antibody was obtained from Calbiochem, Inc.

Statistical analyses were performed by the Student paired (intra-group comparisons, saline vs. albumin) and non-paired (inter-group comparisons) t test. The null hypothesis was rejected at  $p < 0.05$ .

### Results

Plasma volumes were most markedly increased in test subjects receiving albumin and exposed to heat stress although the higher concentration of albumin was no more effective than the low dosage; these elevations were most notable between 1 and 12 h after completion of the infusion. For example, for Ss receiving 25 g albumin and at 37°C, the mean increment in plasma volume over the five sampling times (i.e. 1,3,6,9, and 12 h post-infusion) was  $440 \pm 31$  ml ( $\bar{X} \pm$  SE); with saline,  $159 \pm 43$  ml ( $p < .01$ ). For the high doses of albumin (50 g) and saline (200 ml) the corresponding values were  $429 \pm 32$  and  $144 \pm 17$

( $p < .001$ ). At  $25^{\circ}\text{C}$  25 g albumin elicited a mean elevation of  $296 \pm 6$  ml; 100 ml saline,  $109 \pm 36$  ml ( $p < .001$ ). Corresponding elevations for 50 g albumin and 200 ml saline were  $352 \pm 26$  and  $149 \pm 11$ , respectively ( $p < .001$ ). Without exception volumes had returned to approximately baseline levels after 24 h.

Fig.1 demonstrates the effects of albumin or saline administration on circulating levels of cortisol at  $25^{\circ}\text{C}$  ( $n = 4$ , both dosages) and  $37^{\circ}\text{C}$  ( $n = 7$ , 100 ml Sal;  $n = 6$ , 100 ml Alb;  $n = 9$ , 200 ml Sal;  $n = 8$ , 200 ml Alb). A clearly defined circadian periodicity is observable under all conditions with lowest concentrations occurring in the evening sample (12 h post-infusion, approximately 2100 h) and highest levels manifest in morning samples (approximately 0800 h). For all groups under all conditions mean ( $\pm$  SE) cortisol level at 2100 h (12 h) was  $5.3 \pm .2$   $\mu\text{g}/100$  ml and at 0800 h (0 h),  $17.4 \pm 1.2$   $\mu\text{g}/100$  ml ( $p < .001$ ). For the most part neither plasma volume expansion nor heat exposure had any demonstrable effects upon plasma cortisol levels. There does occur a decrement ( $p < .05$ ) in cortisol levels (noted in the lower left quadrant) 9 hours after albumin administration ( $25^{\circ}\text{C}$ , high dosage); however, no physiological significance appears to be attributable to this difference since no differences are noted at any of the other sampling times.

The effects of plasma volume expansion and heat exposure on aldosterone levels are plotted in Fig. 2. As noted in plasma cortisol levels, there is a periodic oscillation in aldosterone concentrations which appears to follow the general pattern of adrenocortical activity: lowest levels from mid-afternoon (6 h) to evening (12 h), highest during the early morning hours (0 and 24 h). For example, for all groups under all conditions the pre-infusion sample (0800 h) manifests a mean value of  $8.8 \pm 0.9$  ng/dl while 12 h post-infusion (2100 h) this value falls to  $4.3 \pm 0.3$  ng/dl ( $p < 0.001$ ). It is noteworthy that for both dosages and both environmental conditions there occurs a highly significant ( $p < .001$ )

decrement in circulating levels of aldosterone in test subjects receiving albumin. While intersubject variation and patterns are markedly dissimilar, we did observe consistent intraindividual responses which are most manifest in the lower levels and attenuated periodic oscillations of circulating aldosterone in that group of test subjects who received the higher dosage and volume at 25°C. Generally, this group had remarkably consistent, albeit reduced, levels when they received either albumin or saline.

Fig. 3 depicts the effects of plasma volume and heat exposure on circulating levels of angiotensin I. In the 24 h subsequent to infusion there appear to be no demonstrable effects of albumin administration, plasma volume expansion, or heat exposure on levels of this hormone. As observed previously, intraindividual values display a notable consistency while interindividual variations are more marked. No diurnal/nocturnal rhythms in concentration were observable.

Circulating levels of arginine-vasopressin (antidiuretic hormone) are illustrated in Fig. 4. Of the four hormones investigated interindividual variations were most marked for this one. This is particularly noticeable when comparing the results for the two groups of test subjects receiving the low dosage and volume. However, intraindividual values between the saline and albumin administration at each of the two temperatures are very consistent. No effects of albumin administration or heat exposure were noted nor were there apparent any periodic oscillations in levels of this hormone.

### Discussion

In their early review on the endocrinological responses to heat stress Collins and Weiner (6) noted that the adrenocortical response to elevated environmental temperature may be affected by accompanying exercise,

humidity, acclimatization, and alterations in hepatic clearance rate. Later, Collins et al. (5) did report a stimulation of adrenocortical activity when unacclimatized men were exposed to an ambient temperature of 46°C dry bulb, 36°C wet bulb. Indeed, some of our own earlier work demonstrated increments in circulating cortisol levels when high humidity (90%) was added to a moderate heat stress (35°C) (14). In a subsequent heat acclimatization study, however, we (15) observed no effects on cortisol concentrations of moderate exercise (3.5 mph, level treadmill, 90 min) at an ambient temperature of 49°C when the humidity was maintained at 30-35%. In an earlier study Leppaluoto et al. (21) observed no alterations in ACTH levels when men were exposed to extreme heat (100°C); they attributed this lack of response to an accustomization effect as the test subjects were experienced sauna devotees.

The heat conditions imposed upon the test subjects in the current experiment (37°C dry bulb, 25°C wet bulb) clearly had no effects upon adrenocorticotrophic secretion as manifested in circulating cortisol levels. It is somewhat surprising that the combined stress of heat exposure and plasma volume expansion by administration of 50 g albumin was not sufficient to alter in any way the finely controlled nocturnal/diurnal oscillations of cortisol levels. In an earlier study of moderate cold exposure (13) we were able to demonstrate significant alterations in cortisol periodicity in the absence of any noteworthy increase in adrenocorticotrophic activity. From the present results we concluded that acute sedentary exposure to dry heat with accompanying 15% expansion of plasma volume had no effects on the level or periodicity of plasma cortisol.

Follenius et al. (11) have demonstrated that acute exposure of sedentary men to heat stress (46°C) was effective in inducing significant elevations in plasma aldosterone levels. These workers, as well as Bailey et al. (1), reported

that the imposition of a low sodium diet enhanced the response of plasma aldosterone levels to acute heat stress. Kosunen et al. (19) demonstrated significant elevations in plasma aldosterone after just 20 minutes exposure to 85-90°C. It should be recalled that the conditions of the present experiment were more moderate than the aforementioned; further, our volunteers were not fed diets with restricted sodium content. Our present experimental conditions did not prevent the normal reduction in aldosterone levels occurring between 1000 h and 2100 h. However, we did observe a generalized (both dosages and environments) and significant reduction in aldosterone levels after albumin infusion. This could be part of an acute mineralocorticoid response to the increase in plasma volume noted when Ss received albumin.

Several investigators (1,19) have documented a close association between the aldosterone and plasma renin activity (angiotensin I) responses to acute heat exposure. In fact, Finberg and Berlyne (9) reported that following natural heat acclimatization, increments in both hormones were similarly attenuated following further exposure to heat stress. The present data indicated that the acute nature of the heat stress and plasma volume expansion placed on the test subjects was insufficient to elevate angiotensin I levels, although minor inter-group differences were noted.

There have been several reports documenting the relationship between secretion of angiotensin I and arginine-vasopressin (17,18). Results of the present study indicate that neither hormone is affected under these conditions. In their paper Convertino et al. (7) suggested that adaptive elevations in arginine-vasopressin levels may be more closely associated with the chronic increments in plasma volume elicited by consecutive days of exercise training rather than sedentary heat exposure. These workers demonstrated (7) that plasma volume was expanded by 177 ml in the sedentary group (42°C, 8 days) and

by 427 ml in the exercising group (60%  $\dot{V}O_2$  max). Of course, the current experiments combined acute heat exposure with sedentary activity.

Fortney et al. (12) have reported recently that diuretic-induced hypovolemia and albumin-induced hypervolemia were effective in modulating sweat loss during exercise in the heat; however, hormonal responses were not reported in this study.

We have concluded from the present investigations that plasma volume expansion and 24 hours of subsequent exposure to environmental heat stress had relatively minor effects on cortisol and fluid regulatory hormones. Indeed, the finely-controlled diurnal/nocturnal periodicity of cortisol and aldosterone secretion was unaffected although there did occur a significant decrement in aldosterone levels in subjects receiving albumin. The absence of effects on angiotensin I and arginine-vasopressin confirms the importance of other factors (e.g. exercise, heat intensity, exposure time) in eliciting responses of these hormones. Evidently, the expansion of plasma volume was entirely accomplished by the oncotic effects of the administered albumin without endocrine modulation.

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### Disclaimers

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on use of Volunteers in Research.

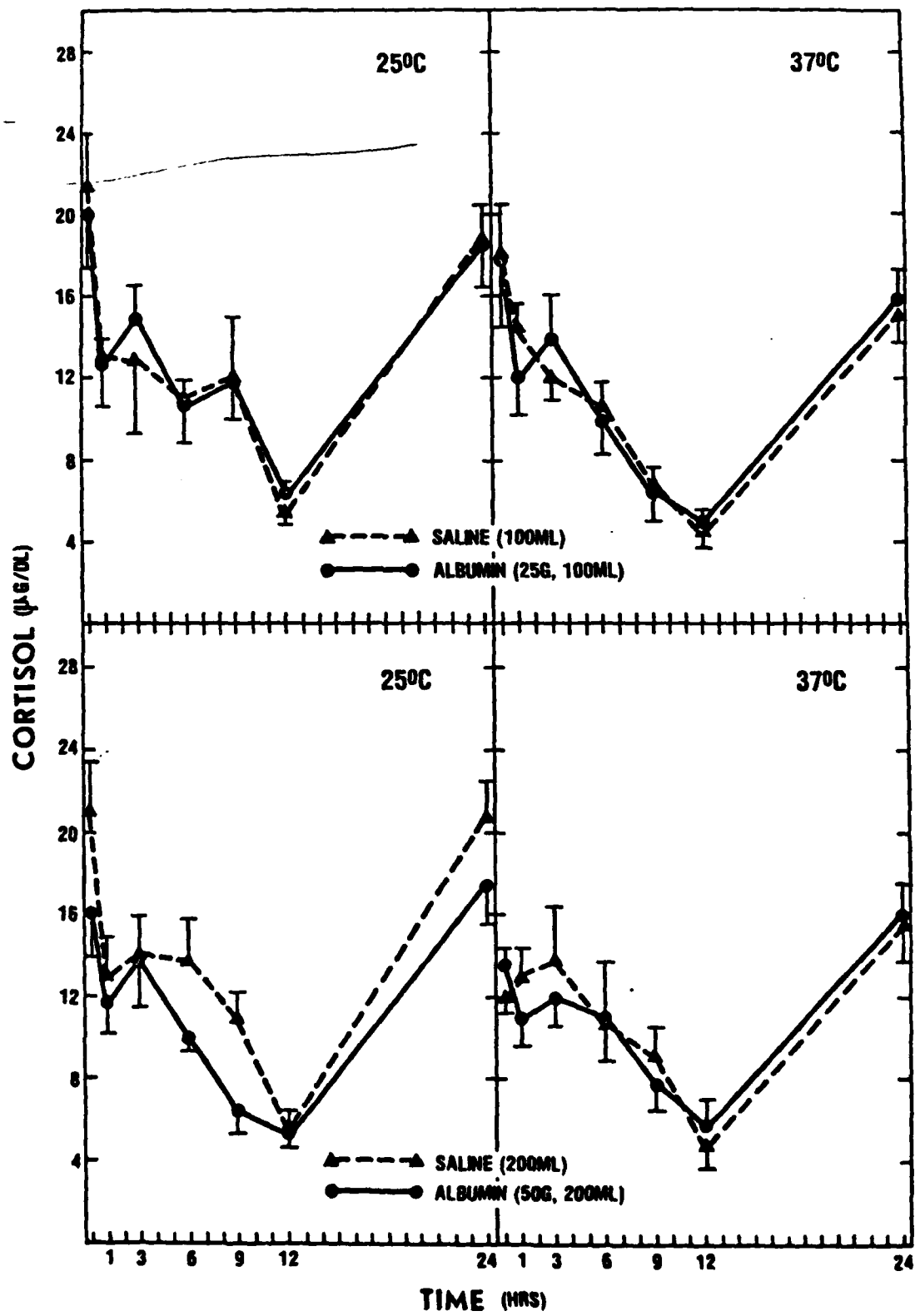
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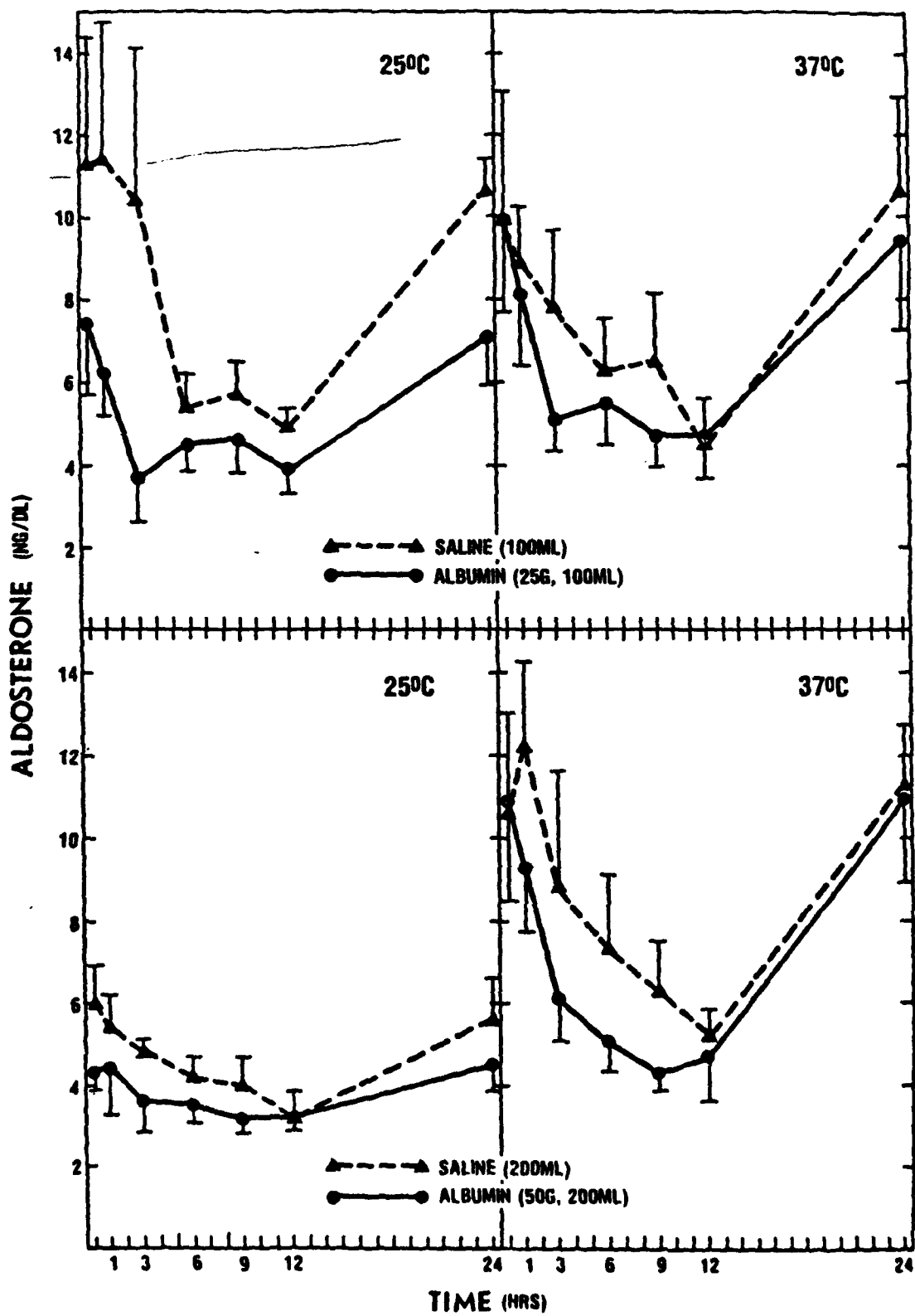
**Fig. 1.** Effects of acute heat exposure and albumin-induced plasma volume expansion on plasma levels of cortisol in samples taken immediately prior to and 1,3,6,9,12 and 24 h following completion of infusion. Sterile, non-pyrogenic saline was administered equivolumetrically under both environmental conditions. Mean values  $\pm$  SE are reported for  $n = 4$  in all experiments conducted at  $25^{\circ}\text{C}$ ; at  $37^{\circ}\text{C}$   $n = 7$  for Ss receiving 100ml saline;  $n = 6$  for Ss receiving 100ml albumin;  $n = 9$ , 200ml saline;  $n = 8$ , 200ml albumin.

**Fig. 2.** Effects of acute heat exposure and albumin-induced plasma volume expansion on plasma levels of aldosterone. All conditions are identical to those specified under Fig. 1 except at  $37^{\circ}\text{C}$   $n = 9$ , 100ml saline;  $n = 10$ , 100ml albumin;  $n = 10$ , 200ml saline,  $n = 10$ , 200ml albumin.

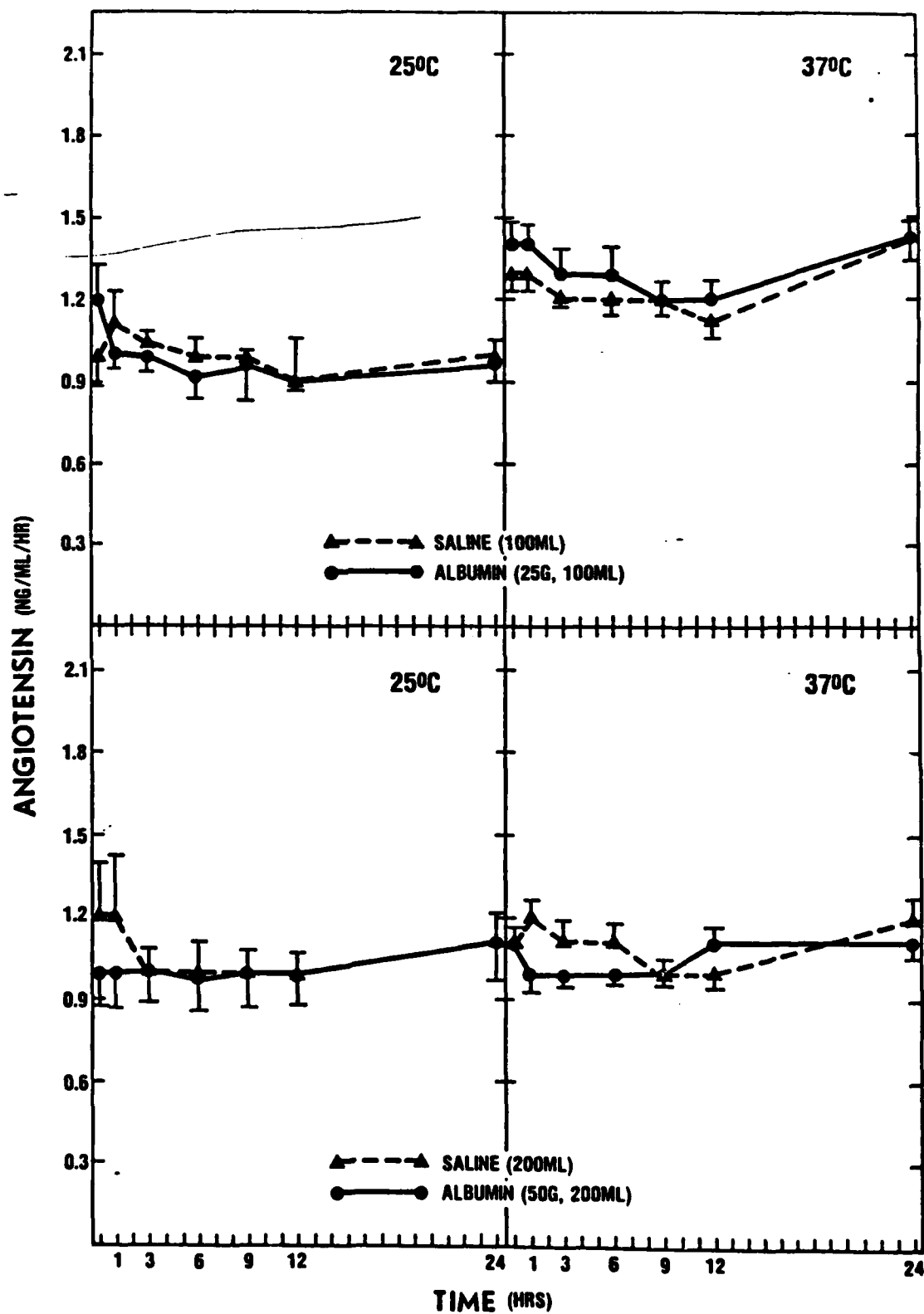
**Fig. 3.** Effects of acute heat exposure and albumin-induced plasma volume expansion on plasma levels of angiotensin I (plasma renin activity.) All conditions are as noted under Fig. 2.

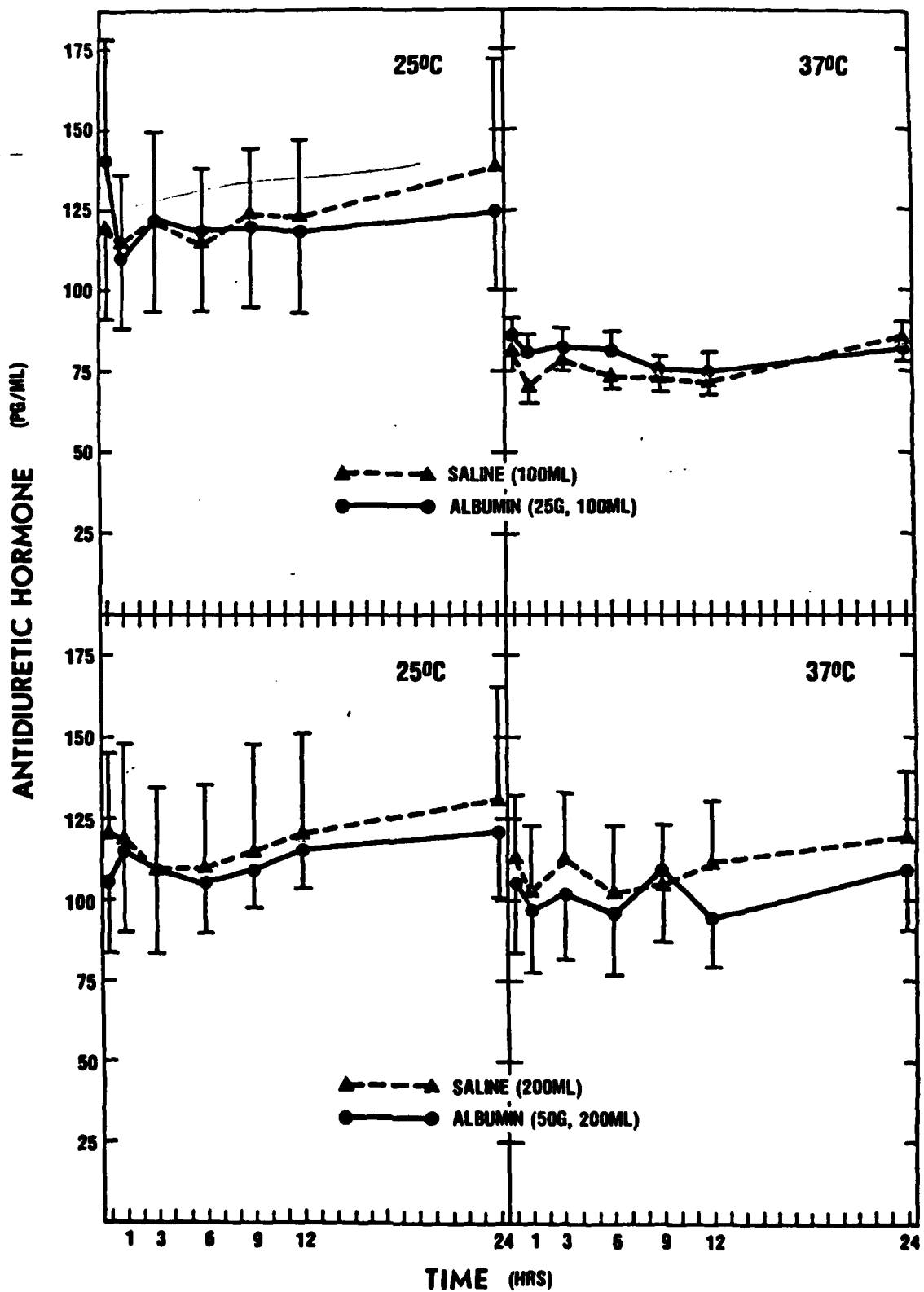
**Fig. 4.** Effects of acute heat exposure and albumin-induced plasma volume expansion on plasma levels of arginine-vasopressin (antidiuretic hormone). All conditions are as specified under Fig. 2.











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2. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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